DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
FEDERAL SECURITY AGENCY
PUBLIC HEALTH SERVICE
LEXINGTON, KENTUCKY

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IN REPLYING, ADDRESS THE
MEDICAL OFFICER IN CHARGE
PUBLIC HEALTH SERVICE HOSPITAL

NIMH Addiction Research Center

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As you undoubtedly know, I had a visit week before last from Mr. Kornetsky. We went over the data obtained so far, and are in the process of making duplicates of the graphs in the dose-effect experiment.

Since Mr. Kornetsky has been here, we have completed another tolerance experiment. In this experiment patients were given LSD for eight days in doses increasing from 20 mcg. to 75 mcg. once daily at 9 a.m. On the ninth day, the 75-mcg. dose was repeated. The results appear in Table I. As expected, a considerable degree of tolerance was developed to the subjective effects of LSD-25. Patients gave an average of only 18 positive answers, as compared to 88 positive answers after three days of water. The clinical grade after eight days was estimated as 0.625 as compared with 1.7 after three days of water. In scoring a number of positive answers and clinical grades, the same criteria were used as described in my prior letter. The grade of tolerance, however, taking into account the individuals concerned, does not appear to be any greater than that developed after three days on two small doses daily (see prior report). Moreover, patients on the eight-day schedule reported more side effects as tolerance was developing, more particularly in the middle part of the schedule.

We have some preliminary information on attempts to break through the LSD-tolerance by increasing the dose. The number of patients is not yet sufficient to permit any conclusions but, however, the information is being submitted for what it is worth, since it is not likely that I will be able to do more prior to the federation meeting.

In one experiment, 4 patients were made tolerant by the three-day schedule (10, 20, and 30 mcg. LSD-25 at 9 a.m. and 9 p.m.), the test dose being given on the fourth day. Two of the patients received a 100 mcg. test dose (increase of 33 per cent) and 2 received 125 mcg. (an increase of 66 per cent). No significant "break-through" occurred in any of these 4 patients.

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Does like a break-up + 2,3 mgs at the time? 20-150 then 200-250 mgs

In another experiment 6 patients were made tolerant, using a nine-dose schedule (one dose of LSD-25 daily at 9 a.m., increasing from 20 to 75 mcg. on the eighth day). On the ninth day, one patient was tested with 100 mcg. and 5 were tested with 125 mcg. There was no significant break-through with either of these doses, although in one patient (DEL) partial break-through was achieved. These series of experiments will be completed as soon as possible, after which we will go on to even higher doses. At the moment, the trend appears to indicate that the dose must be increased more than 66 per cent to restore the original effect of LSD-25, once tolerance has been developed.

I think it is of some interest and some practical importance that we have now tested more than 50 former morphine addicts with LSD-25 (this number includes the group tested in 1951). The important thing seems to be that the mental effects observed in this population are, so far as I can tell from the literature, identical with those observed in other populations, despite the fact that my group differs so greatly with respect to race, economic and educational status, personality characteristics, and prior drug use.

I would like your advice concerning our plans for the immediate future. I have 8 patients checking into the ward next week. This group is made up of individuals who have been in the dose-effect experiment and in the previous tolerance experiment. My objectives are, (1) to corroborate the results obtained with questionnaire and clinical mental examination, using our objective measurements, (2) to determine the break-through dose, using these objective measurements, (3) to test the SKF metabolic blocker for enhancement of the LSD effect, and for its effect during tolerance, (4) to determine the speed of loss of tolerance, and (5) to obtain data on the effect of LSD on the MMPI and Rorschach tests.

The main thing is that to attain all these objectives will require four and one-half to five months; or in other words the experiments will continue until August or September. The decision that must be made is whether these are the most important things for us to do at this time.

Sincerely yours,

Harris Isbell, M.D.
Director of Research

HI:sn

Attachments
cc: Mr. Kornetsky

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TABLE I

TOLERANCE TO LSD-25 -- Eight Day Schedule

75 mcg. Test Dose

PATIENT	After 3 Days H_2O		After 8 Days LSD 20 mcg. increasing to 75 mcg
	No. positive Answers	Grade	No. positive Answers	Grade
SIM	34	1	23	1
DEL	97	3	16	1
WEI	167	3	38	1
FO	18	1/2	2	0
SM	251	3	24	1
GR	5	0	5	0
DO	32	1	31	1
AU	101	2	4	0
Total	705	13-1/2	143	5
Average	88	1.7	18	0.625
HU*			0	0
SH*			2	0

* Control not yet obtained

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TABLE 2

"BREAK-THROUGH"- LSD TOLERANCE

3-Day Schedule

PATIENT	After 3 days H_2O Test Dose		After 3 days LSD 75 mcg. Test Dose		After 3 days LSD Break-through 100 mcg. Test Dose	
	No. pos. Ans.	Grade	No. pos. Ans.	Gr.	No. pos Ans.	Grade
GR	5	0	1	0	9	1/2
AU	101	2	10	0	2	0
					125 mcg. Test Dose	
HU*					7	1/2
DO	15	0	32	1	2	0

TABLE 3

"BREAK-THROUGH" - LSD TOLERANCE

8-Day Schedule

PATIENT	After 3 Days H_2O Test Dose 75		After 8 Days LSD Test Dose 75		After 8 Days LSD Test Dose 100	
	No. Pos. Answers	Grade	No. Pos. Answers	Grade	No. Pos. Answers	Grade
SM	251	3	24	1	0	0
					Test Dose 125	
FO	18	1/2	2	0	1	0
SH*			2	0	0	0
DEL	97	3	16	1	53	2
SIM	34	1	23	1	15	1
WEI	167	3	38	1	35	1